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Diversity of Organic Synthesis

Scientific Exploration Towards Green Innovations

Zainab Ngaini

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Preface

"Chemistry is necessarily an experimental science: its conclusions are drawn from data, and its principles supported by evidence from facts."

Michael Faraday

This book is written based on the research and consultation work which is garnered during my years as a lecturer, researcher and professor in Universiti Malaysia Sarawak. The book started with outlining the conceptual approach and giving an overview of the importance of fundamental and applied sciences. In the same chapter, it reveals the context and rationale for the students and researchers to embed fundamental chemistry before embarking into research in applied sciences.

Then in the next chapter, a compilation of fundamental research in organic chemistry *via* organic synthesis is discussed. The fundamental science is an outstanding topographical illustration of structural synthetic chemistry related to drug design, liquid crystal study, solid phase organic synthesis and other applications. This chapter outlines the significance of functional groups in the development and production of important compounds with various applications. The chemical description of the compounds is supported by spectroscopic instrumentations, molecular docking, polarizing optical micrograph and many other as described in the chapter.

Chapter Three discusses the green chemistry *via* chemical modification of agricultural waste to provide a clean and healthy environment to living organisms and aquatic life. This chapter summarizes the downstream studies on agricultural waste and overcomes issues related to extraordinary properties of sago which hold promises for future applications. An understanding of the synthetic chemical structures and many of the properties from sago and other waste materials are demonstrated in this chapter. Green methodologies have been reported to overcome the current problems even though they trigger environmental and economic concerns in the chemical society.

Chapter Four highlights the achievements based on research innovation at UNIMAS which resulted in the conferment of R&D awards at national and international levels. Organic synthesis is a broad dynamic science that has continuously developed which leads to unique applications of chemistry in science and technology.

This book ends with the conclusion on fundamental and applied chemistry in Chapter Five. I hope this book provides excitement to scientists in making new discoveries and an understanding of the physical world based on the fundamentals of chemistry. I believe that researchers, scholar and scientists are more enthusiastic about the latest research in chemistry. Herein, many important applications of chemistry in our daily life are highlighted.

Acknowledgements

"Deal gently with people and be not harsh; cheer them and condemn them not".

Prophet Muhammad (PBUH)

The production of this book is a team effort requiring the involvement of many people besides the author, who contributed their hard work and talent to bring this edition to life. Although their names do not appear on the cover of the book, their creativity, time and support have been instrumental in all stages of its development and production.

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My acknowledgement would be imperfect without showing appreciation to the biggest source of my strength, my family Assoc. Prof. Dr Hasnain Hussain and three AFs children (Azreen Farhana, Amir Firdaus and Aleesha Farhana). I thank them for their unconditional support, thus allowing me to follow my dream. I am thankful to them for their motivation, cooperation and incredible contribution in helping me to reach this stage in my life.

I thank the management of UNIMAS, the Ministry of Education Malaysia and other grant providers for their numerous financial support throughout the years, allowing me to broaden the horizon of organic chemistry in UNIMAS.

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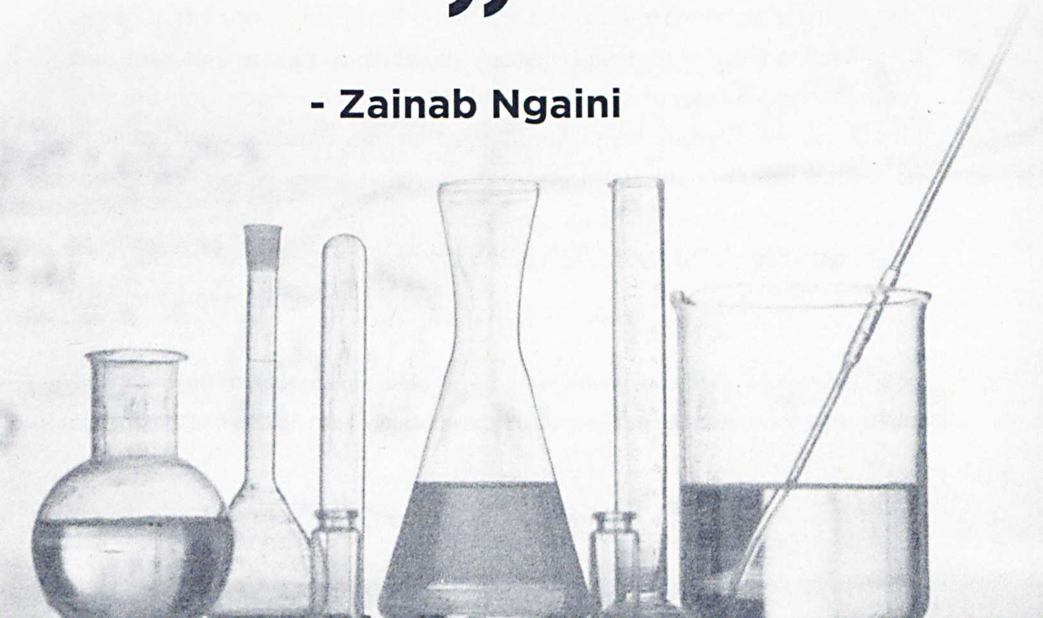
Science triggers your curiosity and builds your character that drives you to greater success.

- Zainab Ngaini



"Understand something. Fall back from the old times and ways of doing things. Chemistry is deeper than the feels."

— **Jill Telford**

Chapter 1

Fundamentals and Applied Sciences

1.1 The Value of Fundamental Research in Chemistry

Chemistry is a branch of science which deals with fundamental information and scientific understanding to further describe how things are modified structurally and chemically for the benefits of mankind. Fundamental research offers benefits in the acquisition of new knowledge, social benefits and economic gains. In fact, new knowledge is the primary product of fundamental research. The social benefits of producing high-quality scientists, technologists and engineers are an immediately recognisable return for the funding of fundamental research. Although it is difficult and even impossible to statistically evaluate the economic returns from fundamental research alone, Martin and Salter (1996) believed that basic research has a substantial impact on productivity where new technology depends on advances in basic research. In other words, funding of fundamental research, especially in organic synthesis, is an investment rather than a cost.

Science is an indispensable field which motivates chemists, researchers and pharmacists to design marketable products to facilitate and improve the quality of humans' life. The design of new methodology using novel reagents, catalysts, solid phase conditions has become a new trend and a very challenging process. The value of fundamental research in the synthesis of novel organic compounds is actively ongoing due to the versatile applications either in pharmaceuticals or in electronic industries. The use of modern instruments such as high-speed ball milling, microwave, ultrasonic irradiations instead of conventional heating is actively ongoing to efficiently achieve the desired products in significant amounts.

1.2 Synthetic Development of Organic Compounds

Fundamental organic chemistry *via* synthesis is an important mechanism in the development of drugs with anti-cancer, anti-bacterial, anti-virus, anti-oxidant, anti-fungal, anti-hyperglycaemic, anti-HIV and anti-depressant properties. New drugs are usually obtained from the derivatisation of naturally occurring compounds in medicinal plants. The collection of the plant samples from a specific location, followed by the extraction and purification of the active compounds, however, is laborious, time-consuming and low in yields. Not all structures in natural products participated in the binding interaction, thus reduces ligand efficiency and pharmaceutical properties.

The search for an effective pharmaceutical drug has become a challenge for researchers due to the inflated cost and times. Chemical modification of medicines from natural product-based molecules has become of interest in recent years. Aspirin is an example of a medicine derived from salicylic acid, a bioactive compound extracted from the bark of willow trees. Salicylic acid was modified into acetylsalicylic acid or aspirin in order to reduce the side effects on the stomach lining (Akay *et al.,* 2008). With this regard, our research approach focuses on the chemical modification of natural product-based molecules as an active scaffolds, which in turn increase their efficiency and the probability of additional interactions with biological targets.

Synthetic chemists usually worked on one reaction, in one reaction vessel at a time to get only one particular product. This method is a less productive, slow and painstaking task as it involves isolation of the product after reaction work-up and purification through crystallization, distillation or chromatography methods. Advancement of the traditional method was introduced *via* combinatorial organic synthesis (Cammidge and Ngaini, 2004) with the aid of robotic or other automation *via* parallel synthesis (Shin *et al.,* 2005). This technique was used to synthesize various type of peptides and carbohydrates. The parallel synthesis technique has also been adapted in the general organic reactions performed on solid phase, typically on resin beads. Often, the reactions applied on various coupling reactions such as Heck, Stille and Suzuki coupling synthesis. In contrast, combinatorial chemistry uses technologies that have potential to make large numbers of products (Cammidge and Ngaini, 2004). Synthetic developments are varied from time to time from conventional oil bath heating to microwave-assisted reaction, ionic liquid phase, ultrasonic, ball-mill and solvent-free reaction at ambient temperature or high pressure. Many current studies reported on microwave reactors and ultrasonic methods due to their convenience, speed, efficiency and high purity compared to conventional heating methods.

Nowadays, governments around the world seem to believe that placing an emphasis on applied research will lead to national wealth creation. In doing so, they are undervaluing the contributions made by fundamental research. Lack of fundamental research could elevate the nightmare of every scientist as evident in the prion disease scrapie research, which had left scientists unprepared to cope with the bovine spongiform encephalopathy (BSE) epidemic and related human diseases in the United Kingdom.

Currently, fundamental research in organic chemistry is moving towards industrial needs. Organic compounds have become important materials and are employed in several usages such as precursors in the preparation of optoelectronic, superconductors, photo sensors and chemosensors. Having fundamental knowledge in chemistry could bring organic synthesis to a higher level. On the verge of the Industrial Revolution 4.0, our research is now enhancing the scope to the synthetic development of organic compounds towards automation, digitization and optimization of liquid crystals studies, optical storage as well as drug designed *via* molecular docking interaction of drug-enzyme.

"An experiment is a question which science poses to Nature, and a measurement is the recording of Nature's answer."

– **Max Planck**

Chapter 2

Fundamental Research *via* Organic Synthesis

2.1 Curiosity Driven in Fundamental Research

There are many arguments over the distinction between fundamental and applied research. Fundamental research in one discipline could easily be construed as applied research in a different discipline. It is also undeniable that basic discoveries in one field may represent applications of existing knowledge in another. In practice, fundamental research has led to many important applications that, almost without exception, were not anticipated at the time when the work was undertaken. In many instances, most applications cannot be foreseen due to lack of modern facilities which build a huge gap between fundamental discovery and eventual applications, which effected the desired demand of investors criteria.

Our fundamental study focuses on the synthesis of organic compounds for various applications in the pharmaceutical and electronics industries (*i.e.* liquid crystal, optical storage and light-emitting diodes). Over the centuries many antibacterial drugs were used to treat bacterial-causing diseases including food poisoning, pneumonia and intestinal infection. The improper use of the drugs has caused the bacteria to evolve into drug-resistant bacteria (Nordin *et al*, 2018). This, in turn, has caused many new drugs to fail in the clinical trials due to poor bioavailability or pharmacokinetics.

The search for an effective pharmaceutical drug has become a challenge for researchers due to the inflated cost and time. The use of medicinal chemistry approaches to modify known drugs seem to be more *via*ble and practical (Ngaini and Mortadza, 2018). In this regard, synthetic and naturally occurring compounds such as chalcone **(1)**, thiourea **(2)**, azobenzene **(3)** (**Figure 2.1**), aspirin, coumarin and their derivatives have been extensively studied and developed as one of the pharmaceutically important molecules (Farooq *et al.*, 2019 ; Ngaini and Mortadza, 2018). Chemical manipulation of an active scaffold from the naturally occurring compounds from plant and natural product-based molecules have also been employed in the preparation of compounds with other applications such as liquid crystals, dye synthesised solar cells, optical storages and fire retardants, which are discussed in this chapter.

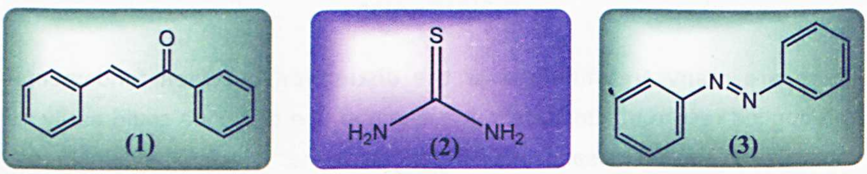


Figure 2.1: Chalcone, thiourea and azobenzene

2.2 Chalcone and Their Derivatives

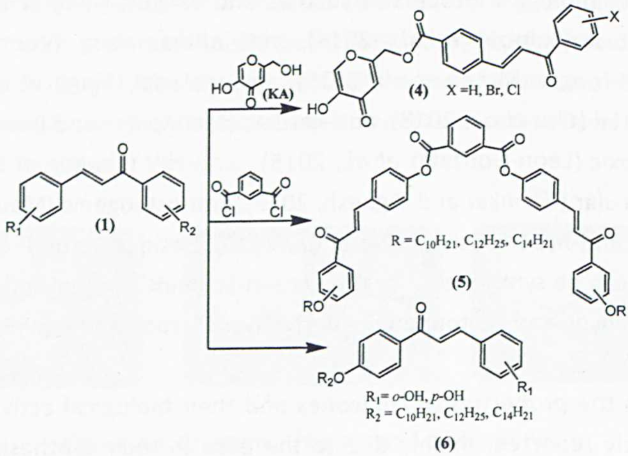
In organic chemistry, synthesis and structure manipulation of natural product-based molecules are able to increase the probability of additional interactions and strong binding towards the target molecules due to the easy availability of active sites. Our fundamental research is based upon naturally available compounds commonly derived from natural resources.

Chalcone is a naturally occurring yellow compound that is isolated from natural resources such as soy, tea, safflower, fruits and vegetables. It is present in almost every part of plants from leaves, flowers, fruits and woody tissues (Barros *et al.,* 2004). Chalcone is an important intermediate in the biosynthesis and synthesis of many pharmaceutical products such as flavanones, flavones, isoflavones, pyrimidine, pyrazole, indazole, indole, pyrazoline, epoxide, oxazole and aurones. Generally, chalcone consists of two aromatic rings and three carbons containing α, β-unsaturated keto group, having two structural isomeric form *cis* and *trans*. *Trans*-isomer is thermodynamically more stable in comparison to *cis*. This class of compound can be found naturally, readily synthesized and even semi- synthesized.

Chalcone **(1)** and its derivatives have been reported to possess a broad spectrum of biological properties such as anti-oxidant (Jung *et al.,* 2017), anti-microbial (Sulpizio *et al.,* 2018), anti-inflammatory (Verma *et al.,* 2018), anti-fungal (Matos *et al.,* 2015), anti-malarial (Singh *et al.,* 2014), anti-bacterial (Chu *et al.,* 2018), anti-cardiac (Mahapatra and Bharti, 2016), anti-cytotoxic (Leon-Gonzalez *et al.,* 2015) , anti-HIV (Zhuang *et al.,* 2017), anti-tubercular (Gaonkar and Vignesh, 2017), anti-osteogenic (Maurya *et al.,* 2018) and anti-hypertensive (Silva *et al.,* 2013). Besides natural extraction, chalcones can be synthesized *via* the Claisen-Schmidt condensation reaction of benzaldehyde and acetophenone derivatives (Farooq and Ngaini, 2019).

Studies on the properties of chalcones and their biological activities have been widely reported, mainly due to the ease in their synthesis and the versatility of the chalcone moiety (Ngaini *et al.,* 2014a). Our research team is actively working on chalcones and employed as an active scaffold in the development of other derivatives by introducing active groups to the molecular framework. The introduction of important functional groups such as hydroxyl (OH), carbonyl (C=O), ester (C=OOR) moieties (Ngaini *et al.,* 2014b) and aliphatic substituents (-CH_2)- on the chalcones derivatives **(4-6)** has resulted in excellent biological activities (**Scheme 2.1**) (Ngaini *et al.,* 2009; Ngaini *et al.,* 2010) as compared to that of the standard drug, ampicillin.

The search for a lead product with beneficial pharmacological properties has become a great challenge and costly. Extraction and synthetic modification of bioactive compounds from natural resources have gained great attention and found to be cost-effective. Incorporation of chalcone with other biologically active compounds derived from natural products such as kojic acid (KA) has enhanced the biological activities (Ngaini *et al.,* 2014a). KA is a natural heterocyclic pyrone having two double bonds with significant biological activities in medicine and pharmacological field (Zirak and Eftekhari-Sis, 2015). KA is slightly acidic and easily produced *via* fungal fermentation from various types of carbon substrates. The incorporation of KA onto chalcone network **(4)** has synergistically transformed the lipophilic properties of chalcone for excellent pharmaceutical properties (**Scheme 2.1**) (Sie *et al.,* 2018). A good balance between hydrophilic and hydrophobic properties of compound makes up for good antibacterial agents.



Scheme 2.1: Synthesis of chalcone derivatives

Chalcones are florescent, stable compounds which contribute to the synthesis of various pharmacologically important heterocyclic structure-based derivatives (Farooq and Ngaini, 2019). The chemical reaction of chalcone with inorganic compound such as cyclotriphosphazene derivatives **(7 & 8)** (**Figure 2.2**) was employed as luminescent materials in electronics (Ngaini and Abdul Rahman, 2010a), liquid crystal displays (Ngaini and Abdul Rahman, 2010b; Abdul Rahman and Ngaini, 2011), optoelectronic devices (Koran *et al.,* 2016) photolithography (Allcock *et al.,* 1995) and biological applications such as anti-tumour (Görgülü *et al.,* 2015), anti-bacteria agents (Jiang *et al.,* 2015), and as microencapsulation materials (Allcock *et al.,* 1995).

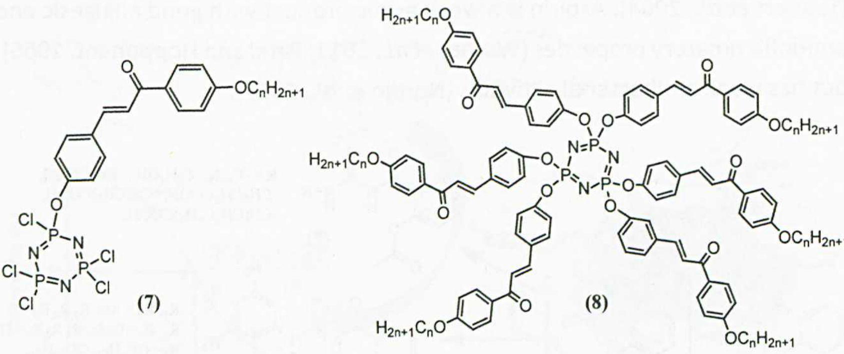


Figure 2.2: Mono and hexa substituted chalcone based cyclophosphazene

2.3 Thiourea and Their Derivatives (N=C=S)

In a drug discovery process, the derivatization of synthetic or naturally occurring scaffolds from plants is highly relevant as such molecular changes are able to provide new insights into the bioactivities and structure-activity relationships against the specific targets. Removing the unnecessary moieties, chirality and stereochemistry make the derivatives of organic scaffolds become convenient and economical to be synthesized. Synthesis and individualized structure manipulation of natural product-based molecules are able to raise the probability of additional interactions and strong binding to the active sites. Thiourea is an organic compound, which consists of thiocarbonyl and amine groups (NH, C=S, C=O) (Ngaini *et al.,* 2013a), is known to display broad range of biological properties such as antibacterial (Abd Halim and Ngaini 2017; Nordin *et al.,* 2017).

The incorporation of reactive thiourea **(2)** into the natural product-based network such as aspirin, *via* reaction of acetoxybenzoyl thiocyanate with a series of anilines, is able to produce mono-thiourea derivatives with a promising new biological activities such as antibacterial **(9 & 10)** (Ngaini *et al.,* 2012a; Ngaini *et al.,* 2017b) and anticancer agent **(11)** (Nordin *et al.,* 2018) **(Scheme 2.2)**. Aspirin (ASA) is a bioactive compound derived from salicylic acid, which was extracted from the bark of willow trees (Mahdi, 2010). Salicylic acid was modified into aspirin in order to reduce the side effects of this drug on the stomach lining